

A STUDY OF THE CARDIOVASCULAR EFFECTS OF HALOTHANE*

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INTEREST IN THE cardiovascular effects of anaesthetics, and in particular Halothane, was born of frequent operating theatre debates that occurred between surgeons and anaesthetists at a number of hospitals. This interest was rekindled by some basic physiology experiments on arterial blood flow where Halothane was used to reduce flow in intact animals in an empirical way.

In the search for new non-explosive inhalation anaesthetics, Robbins¹ found that some fluoro-hydrocarbons had anaesthetic properties with therapeutic ratios greater than those of ether and chloroform. Raventós² described how his colleague, Dr. Suckling, synthesized Halothane (CF_3CHClBr) and how he and Suckling carried out experiments on the anaesthetic and pharmacological actions of Halothane. Halothane was found to be safe and stable with no post-anaesthetic side effects. With reference to the cardiovascular effects, it was stated that, with the exception of hypotension, it did not produce any serious functional disturbances. It did not produce cardiac irregularities but increased the sensitivity of the heart to adrenaline. It did not increase capillary bleeding. In animal experiments Raventós found an inhibition of contraction of the isolated tortoise atrium, similar to that produced by chloroform and cyclopropane. It took six times as much ether to produce the same effect. In dogs, no change in cardiac output was observed and it was assumed that vasodilatation in the splanchnic area, probably due to a sympathetic ganglion block, was the main cause of hypotension. At first experimental work accumulated to suggest that the main cardiovascular effect of Halothane was vasodilatation. More recently, myocardial depression has been found more dominant. It was the object of this study to attempt to evaluate the cardiovascular effects of Halothane with particular reference to changes in myocardial blood flow. The rate of recovery from the anaesthetic will be demonstrated, implications of the effects upon complications that may beset surgery will be considered together with methods of reversing Halothane depression with the aid of drugs. It is not the aim of this study to denounce Halothane but to stress its cardiovascular effects and underline

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that although it has been accepted in clinical practice it can have dangerous side effects when used in high concentrations. It is suggested that the anaesthetic may have other useful side effects which could be used to advantage.

INTRODUCTION

A number of accepted experimental methods have been used to intensively investigate Halothane in animal tissue preparations, in intact animals, and in human beings in the clinical situation. Initial experiments of this study were carried out using Labrador dogs as experimental subjects. For most of this work a Biotronex electromagnetic flow meter was used to measure blood flow. The effects of Halothane on the canine heart were then compared with the effects of Halothane on the human heart in the clinical situation measured using a new technique requiring minimal interference with the patient.

Before describing these experiments it is necessary initially to consider and evaluate the electromagnetic flow meter used in many of these experiments.

An evaluation of electromagnetic flow probes

A Biotronex electromagnetic flow meter (Model BL/610) was used in conjunction with Biotronex, Series 1,000 flow probes. The principle of operation is that an e.m.f. is induced in a conductor (blood) moving in a magnetic field, at right angles to the lines of force. The magnitude of the induced e.m.f. is a function of the rate of movement (velocity). Early meters were either sine waves or square-wave instruments. The sine wave flow meter offered the advantage of small mass transducers since less magnetic drive is required for a comparable flow signal than is required for square-wave instruments. These instruments were not particularly easy to operate. Square-wave flow meters did not have critical manual gating and were much easier to operate. They did have the disadvantage that a large mass transducer is required to prevent excessive heating. The Biotronex pulsed-logic meter combines the advantage of both sine and square-wave systems. Integrated circuits generate pulses which are used to energize the magnet at the appropriate time. The drive can be made to alternate between two to four transducers, making simultaneous studies possible without interference between units.

Large flow probes required to measure cardiac output were calibrated *in situ* around an excised segment of aorta with saline and canine blood at varying haematocrits using a calibrated roller pump working against a constant head of pressure. Small flow probes used to measure blood flow in peripheral coronary arteries were calibrated using canine blood fed to an excised vessel of a suitable size from a static reservoir

maintained at 100 cm. above the probe. Different flows were obtained by variable resistance distal to the probe. The calibrated probes now had to be compared against standard accepted methods of blood flow measurement.

1. A comparison of cardiac outputs using dye dilution method and an electromagnetic flow meter.

This experiment has already been described in detail³. The results show good correlation between dye injection cardiac outputs and electromagnetic flow measurement. Further statistical analysis did show a better agreement between results from cardiac output assessed from a pulmonary artery flow probe than from an aortic flow probe. This difference is attributed to the difficulty of zero estimation with the aortic flow probe.

2. A comparison of myocardial blood flow measured by a radio xenon washout with coronary artery flow measured by an electromagnetic flow meter

Indicator washout measurements of tissue blood flow have been used for some time. The introduction of radioactive gases in solution now allow the washout rate to be assessed by an external counter. This method of measuring myocardial blood flow has become established in experimental and clinical practice. Again dogs were used as experimental subjects. Results of the electromagnetic flow recordings were converted to flow per 100 grams of muscle and were plotted against myocardial blood flow calculated from the $t_{\frac{1}{2}}$ and peak/area of the xenon washout curves. Figure 1 showed regression lines drawn from the results of three experimental animals.

THE EFFECTS OF HALOTHANE ON THE CARDIOVASCULAR SYSTEM OF THE DOG WITH SPECIAL REFERENCE TO CORONARY BLOOD FLOW

Method

Fourteen Labrador dogs, weighing 17 to 24 Kg., were used in this study. Without pre-medication they were anaesthetized with sodium thiopentone (20 mg./Kg.) and ventilated with nitrous oxide (ratio 2:1) through an endotracheal tube using a modified Starling pump. The pump rate was 28 per minute and the stroke volume was set at 10 ml./Kg. with an increase of 50 ml. after thoracotomy. Further small adjustments were made to maintain the arterial P_{CO_2} at 40 mm. of mercury. Halothane was administered, using a Fluotec vaporizer, and the inspired gases were continuously sampled through a Hook and Tucker ultraviolet analyser. An intravenous infusion of 0.9% sodium chloride was administered to replace insensible fluid loss at a rate of approximately 100 ml./hour. Oesophageal temperature was recorded

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so that adjustments could be made where necessary. Nylon cannulae were placed in the central aorta, by way of the left femoral artery, and in the right atrium, by way of the left jugular vein, and pressure recorded through Statham P239 transducers. A Cournand catheter was introduced via the left jugular vein to the coronary sinus under X-ray control and placed 4 cm. into the great cardiac vein. The electrocardiogram was monitored, using needle electrodes.

Through a left lateral thoracotomy, previously calibrated Biotronex Series 1000 flow probes of the appropriate size were placed around

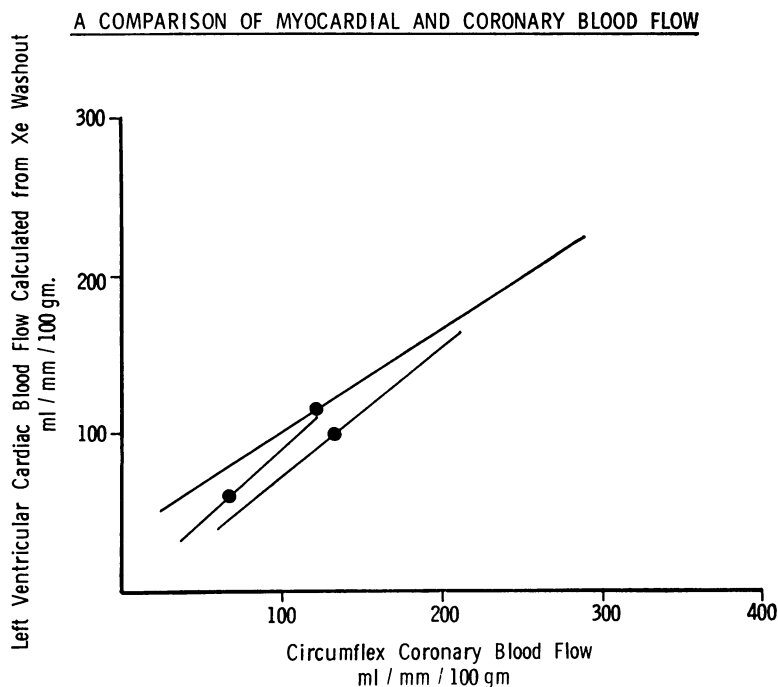


Fig. 1. Regression lines drawn for each of the three dogs.

the pulmonary artery to measure cardiac output, and the circumflex coronary artery to estimate myocardial blood flow. A third probe was placed on the right femoral artery. Snare to produce zero flow were placed on the circumflex coronary artery and femoral artery, distal to the flow probes. Recordings were made on an eight-channel Sanborn Direct Writer, Series 315. At intervals, blood samples from the coronary sinus, right atrium and central aorta were taken for haematocrit, haemoglobin content and analysis of blood gases, using the Astrup microtechnique and the Siggaard Anderson nomogram and an oxygen electrode Po_2 was converted to percentage saturation using the

appropriate corrections for temperature, pH and base excess. Using haemoglobin content the quantity of oxygen per 100 ml. of blood was calculated for the three blood samples. It is appreciated that right atrial blood may not always be representative of mixed venous blood, but samples compared favourably with right ventricular samples which were taken from four of the dogs.

The dogs took between 60 and 90 minutes to prepare for study. Only when a satisfactory stable state had been achieved for at least 30 minutes were experiments carried out. Two dogs were excluded from the series because of blood loss. After satisfactory base line readings, Halothane was administered for a 15-minute period in concentrations of 0.5%, 1%, 2%, 2.5% and 3%. The concentrations of anaesthetic used were given in this order in seven dogs and in the reverse order in the remaining seven dogs. The order in which concentrations were used made no significant difference to the results. Recovery was observed for up to 40 minutes after turning off the Halothane. Only if blood pressure, right atrial pressure, cardiac output, coronary and femoral flow returned to previous control level was the animal subjected to a different Halothane concentration for a further 15-minute period.

TABLE I

% Halothane					Recovery time from Halothane in minutes				
0.5	1.0	2.0	2.5	3.0	5	10	15	20	and over
5	7	10	5	7	4	6	3	11	

No. of results for each group.

From the data obtained the following measurements were recorded or derived from analysis: mean aortic blood pressure, mean right atrial pressure, cardiac output, mean circumflex coronary blood flow, mean femoral artery blood flow, coronary vascular resistance, femoral vascular resistance, total body vascular resistance, quantity of oxygen used by total body and percentage utilization, left ventricular stroke volume, left ventricular work and left ventricular power.

Results

The average weight of the dogs used was 20 Kg. In order to plot the results graphically with a meaningful statistical analysis, corrections for weight were made to blood flow results from the femoral artery and circumflex coronary artery and to cardiac outputs so that all referred to a standard 20 Kg. dog. Mean values are expressed graphically with their standard deviations. The significance, derived from the student *t* test of each graph, is quoted. The mean value of the maximum change in each parameter is also recorded as a percentage of the base line values. The number of readings taken at the various points on the graphs below are recorded on Table I.

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20 Kilo Open Chested Dog. Anaesthetized with N_2O and O_2

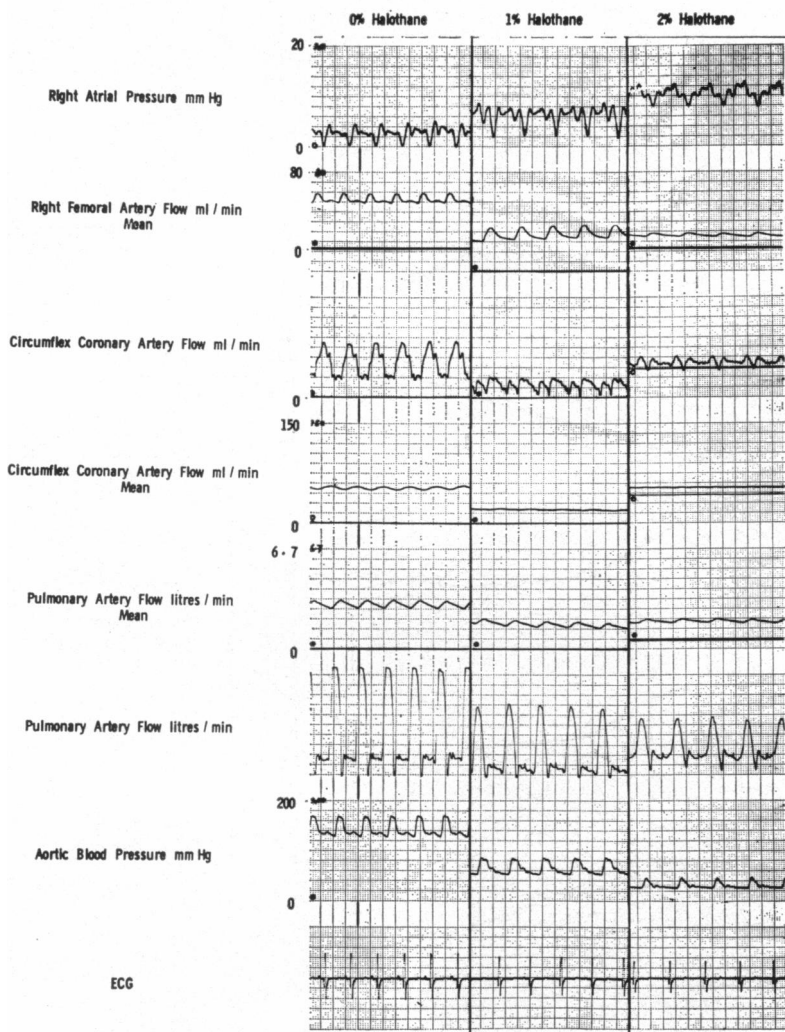


Fig. 2. The typical effect of Halothane as recorded on the chart (calibration of mean and phasic flows in the pulmonary artery and coronary artery on this chart are the same—the calibration is marked on the mean chart only).

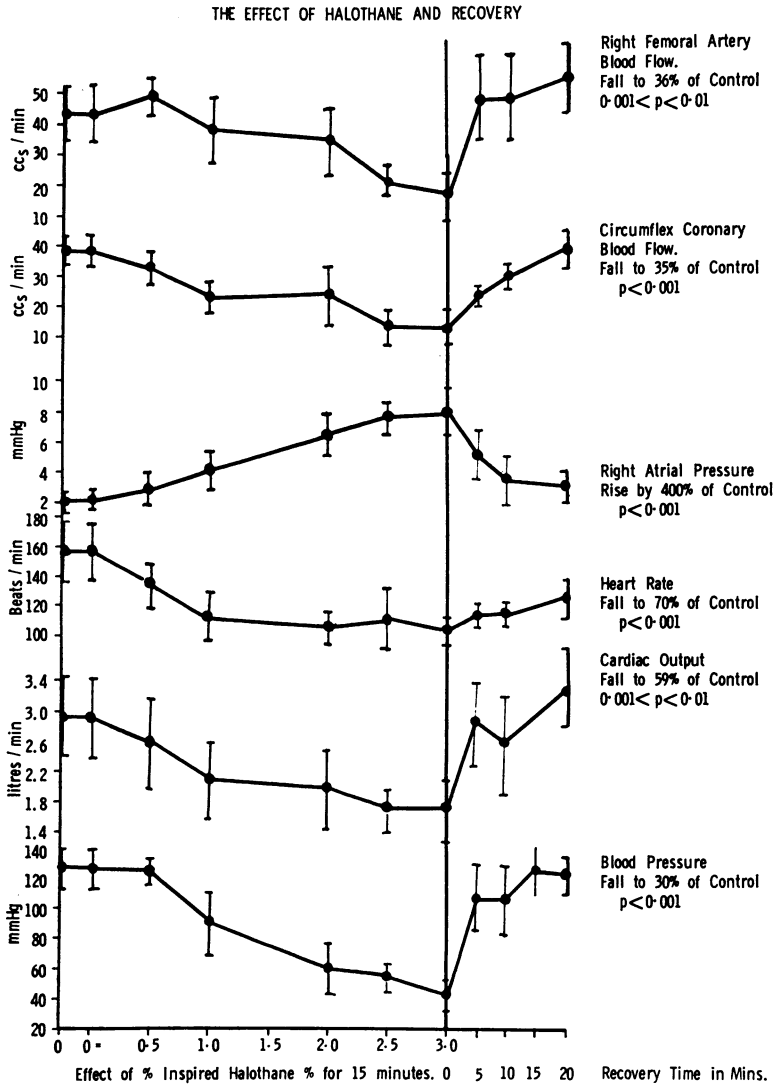


Fig. 3. Graphical representation of the changes in the direct measurements made during the experiments. Mean values are shown as points with their standard deviations.

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Although observations were made up to 40 minutes after Halothane was discontinued, recovery was complete by 20 minutes in 9 of the 11 dogs observed and no further changes occurred beyond this point. After weight corrections were made to the flow readings, values were calculated and statistical analysis was carried out. Mean and control values for the same animals were compared. The Snedecor Variance Ratio (F test) of the results and the base line values were computed after applying Bassell's correction for small sample numbers. Where this was not significant at the 1.5% level the Student *t* test was applied.

Figure 2 shows the typical effect of Halothane as recorded on the chart. Figures 3, 4 and 5 shows the results expressed graphically.

In all the dogs, an increase in heart size and a decrease in systolic emptying was observed as the percentage of Halothane in the inspired gases increased.

Discussion. In a concentration of 0.5%, Halothane has little cardiovascular effect apart from a reduction in heart rate (Fig. 3). In concentrations greater than this there is progressive depression of myocardial function seen in falling heart work, cardiac output and blood pressure (Figs. 3 and 4). Although a decrease in heart rate and fall in total vascular resistance does occur⁴, the major effect appears to be on the heart itself and its progressive failure is underlined by a marked rise in atrial pressure and an observed increase in heart size as emptying in systole deteriorates. Femoral artery and coronary artery blood flow fall by the same order as the blood pressure, there being little change in vascular resistance, particularly in the coronary artery. The quantity of oxygen used per minute by the myocardium falls by the same amount as the coronary artery blood flow. There was no significant change in arterial oxygen saturation while coronary sinus blood oxygen saturation rose, reducing the arterio-venous oxygen difference (Fig. 5). These findings are contrary to those of Saito *et al.*⁵, who found increases in coronary arterio-venous oxygen difference. Eberlain⁶ found decreasing coronary blood flow with increasing Halothane concentrations, but saw no change in coronary sinus oxygen saturation and felt there had been a concomitant decrease in oxygen consumption. The recovery phase of our experiments gave no indication of an oxygen debt. Oxygen consumption returned to the control level over 20 minutes, as did the arterio-venous oxygen difference. Bagwell⁷ and Merrin⁸ were unable to find evidence of excess lactate production in dog coronary sinus blood under Halothane anaesthesia. It must be remembered that the concept of excess lactate as an indicator of anaerobic metabolism has recently been questioned. At whatever level Halothane interferes with the myocardium, available work would seem to show that compensation by anaerobic metabolism is slight if it occurs at all.

Total body oxygen consumption fell by 60% (half the fall shown in myocardial oxygen consumption) and, like the heart, recovery occurred

THE EFFECTS OF HALOTHANE ON THE CANINE HEART

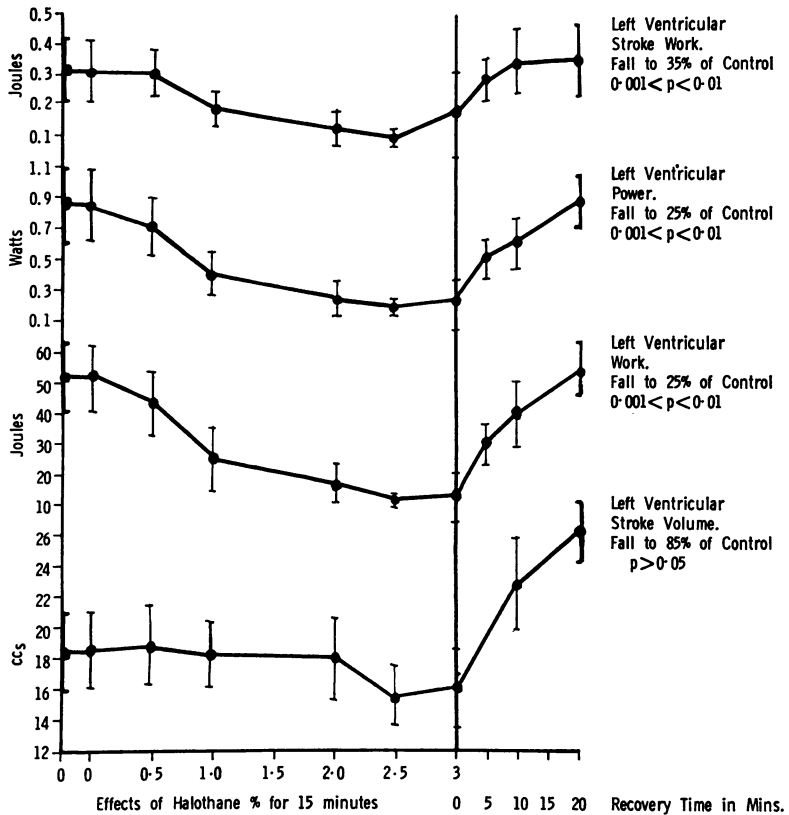


Fig. 4. The graphical representation of the changes in myocardial activity at different Halothane concentrations.

Left ventricular work in joules = (mean aortic pressure - mean left atrial pressure) \times cardiac output \times F

Left ventricular power in watts = Left ventricular work/second.

Left ventricular stroke work in joules = (mean aortic pressure - mean left atrial pressure) \times stroke volume \times F

(F = $1.36 \times 0.981 \times 10^{-4}$ and is the conversion factor for c.g.s. units)

Mean values are shown as points with their standard deviations.

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over 20 minutes with no increase in demand. There was no significant change in pH or base deficit, but if the anaesthetic was given for longer periods of 30 minutes or more, a fall in pH and increase in base deficit was seen, suggesting a degree of tissue hypoxia due either to low flow and pressure, the direct effect of Halothane, or a combination of both.

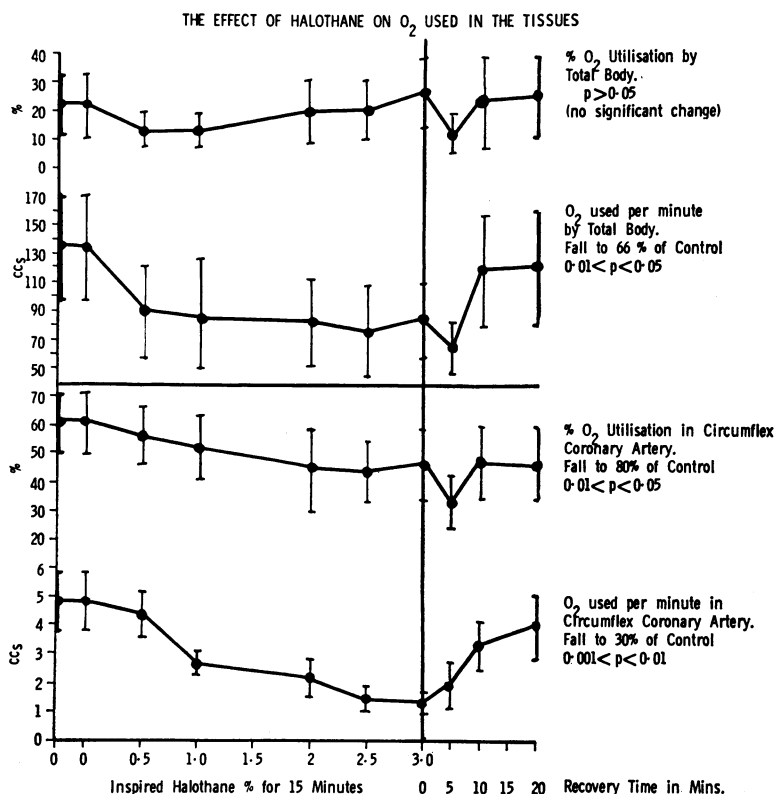


Fig. 5. The effect of Halothane on oxygen utilization by the whole animal and by the myocardium. This is expressed as a percentage of available oxygen and as an absolute figure in c.c. of oxygen used per minute, which takes into account perfusion. (O₂ capacity taken to equal gm. Hb. \times 1.39). Mean values are shown as points. Standard deviations for the mean values are shown.

It is obvious that considerable surgical interference was necessary to carry out this experiment. Stability of the prepared dogs is shown by minimal changes in systemic oxygen utilization (for surgical shock associated with blood loss will give rise to significant increases in the percentage oxygen utilization); the haematocrit and haemoglobin investigations in the experimental dogs fell by no more than 12% in any animal under study.

THE EFFECT OF DRUGS USED IN ANAESTHESIA ON THE CIRCULATION OF THE DOG ANAESTHETIZED WITH HALOTHANE

1. The effect of vagotomy and Atropine

It was found that, in the experimental dogs, blocking vagal activity either by vagotomy or Atropine increases heart rate under nitrous oxide and oxygen anaesthesia and under light Halothane anaesthesia. It made no significant difference to deep Halothane anaesthesia.

2. The effect of Digoxin

The value of prophylactic pre-operative digitalization is not easily determined. In man, assessment of this form of therapy is difficult because exact equivalent chemical conditions are rarely found. Furthermore, the stresses encountered by the cardio-vascular system during operation vary with different surgical procedures and anaesthesia. Boniface and Brown⁹ and Goldberg *et al.*¹⁰ demonstrated that Digoxin protects the dog's heart against the negative inotropic effect of thiopentone and Halothane.

Five dogs prepared in the same manner as the previous experiments were subjected to varying concentrations of Halothane and myocardial function assessed. The animals were then permitted to recover and intravenous Digoxin 0.1 mg./Kg. body weight was given. The first experiment was then repeated. Results indicated that Digoxin did appear to have some value in reducing the negative inotropic effect of Halothane anaesthesia; however, these results did not achieve statistical significance when subjected to a correction for small samples.

3. Calcium

It has been known for many years that myocardial contractility is markedly influenced by variations in calcium concentrations¹¹. Calcium appears to be important for the normal function of excitable membranes. Although it has little effect on resting membranes potential under normal conditions it does modify resting potential changes induced by alterations in extracellular potassium concentrations. The most important effect of calcium on electrical events is on excitability spike and repolarization phenomena. Within muscle, calcium affects the contractility of actomyosin threads and ATPase activity.

In this experiment calcium was administered intravenously to dogs prepared with flow probes as previously described and anaesthetized with Halothane. In four dogs, calcium chloride 0.5 ml. to 2 ml. of a 20% solution was injected intravenously before and after Halothane administration. In animals anaesthetized only with oxygen and nitrous oxide, calcium produced a small short transient rise in blood pressure and cardiac output. It also increased coronary artery and femoral

flow to the same extent. In animals anaesthetized with 2% Halothane for a period of 15 minutes, intravenous calcium chloride produced a marked improvement in cardiac output, blood pressure and heart rate which produced a similar rise in coronary and femoral artery flows. A single injection of 0.5 ml. 20% calcium chloride solution increased blood pressure by 10 to 20%. Cardiac output was increased by 20 to 30% and right atrial pressure fell within the range of control values. It was found that a single administration of a small quantity of calcium chloride solution reduced recovery time after discontinuing Halothane. Recovery time was normally 15 to 20 minutes, which was reduced to 5 to 12 minutes after calcium.

4. Adrenaline and isoprenaline

Arrhythmias and sinus tachycardia are well known during Halothane anaesthesia following the subcutaneous administration of adrenaline. There are, however, reports of the safe use of adrenaline with Halothane anaesthesia. Katz and Katz¹² concluded that many of the reports reported arrhythmias and cardiac arrests occurring with a combination of Halothane and adrenaline could be attributed to rapid administration of too much adrenaline in high concentrations. They also suggested that hypercarbia and/or hypoxia appeared to have been contributory. Adrenaline and isoprenaline in concentrations of 1 in 200,000 and 1 in 500,000 were administered to dogs prepared with flow probes, before and after being subjected to 2% inspired Halothane for a 15-minute period. Short lasting effects were observed with small single-dose injections. It was found possible to reverse the myocardial depression of Halothane with either of these drugs. Arrhythmias occurred with both but were less marked with isoprenaline than with adrenaline. Adrenaline produced a much greater rise in blood pressure but achieved this mainly with intense vasoconstriction. Isoprenaline, on the other hand, permitted a rise in femoral flow proportional to the increase in cardiac output and blood pressure. With adrenaline administration, right atrial pressure rose but with isoprenaline it fell.

5. Propranolol

Propranolol has been successfully used in the prevention and alleviation of cardiac arrhythmias associated with Halothane anaesthesia. In dogs prepared with flow probes and subject to control ventilation as previously, Halothane was administered in an inspired concentration of 2% for 15 minutes before and after 1 mg. of propranolol was injected intravenously. The injection of propranolol produced a 5 to 10% fall in blood pressure and cardiac output. There was no significant increase in right atrial pressure. Results were not conclusive but indicated that, where arrhythmias occurred under deep Halothane anaesthesia, it would be preferable to reduce the level of anaesthesia rather than attempt to suppress the arrhythmia with propranolol.

THE EFFECT OF HALOTHANE ON ASCENDING AORTIC BLOOD FLOW ACCELERATION IN HUMANS

A. Theory and experiments for the use of the pre-injection period

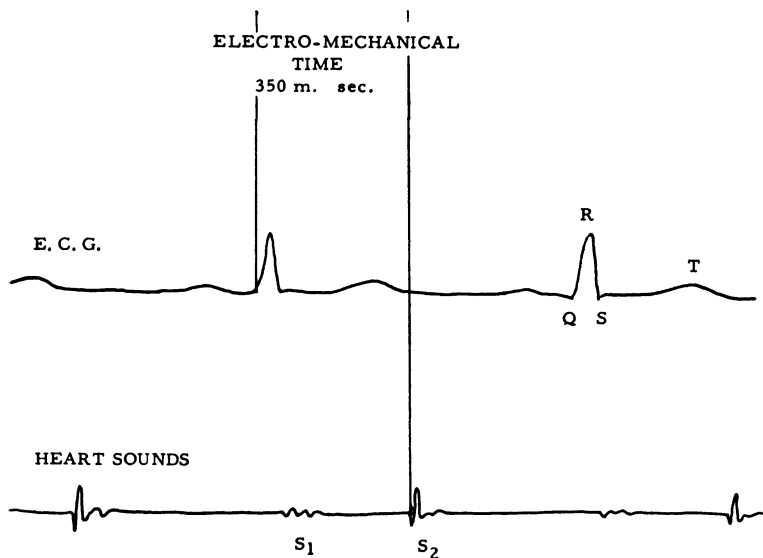
In 1963, Siegel and Sonnenblick¹³ described the mechanics of isometric contraction in the heart. Investigating the maximum rate of development of isometric tension (dp/dt) and the integrated isometric tension (IIT) on a beat-to-beat basis, they concluded that the ratio $\frac{dp/dt}{IIT}$ is a quantitative measure of contractility of the myocardium. In the intact ventricle they found the time of stimulation to dp/dt max. (Δt dp/dt) remained constant with varying pre-load and after-load. The time for aortic flow to reach maximum velocity (V max.) also remained constant with variable pre-load and after-load. V max. was found to be directly proportional to the inotropic state of the heart. Wallace *et al.*¹⁴ and Wildenthal *et al.*¹⁵ found that the peak Δt dp/dt usually occurred at the instant of opening of the aortic valve, at the peak of isovolumetric ventricular pressure. Thus Δt dp/dt is equivalent to the pre-ejection period. A clinical technique for the determination of the pre-ejection period (PEP) from the phonocardiogram, arterial pressure trace and electrocardiogram is described by Weissler *et al.*¹⁶ (Fig. 6).

Reitan *et al.*¹⁷ used the foregoing concept to devise a clinical method for the stimulation of myocardial contractility. The index of myocardial contractility $\frac{dp/dt \text{ max.}}{IIT \text{ (integrated isometric tension)}}$ is described¹³ as being the Iso-metric Time-Tension Index or ITT. Reitan *et al.* point out that this index is a correlate of blood flow acceleration and both share a common temporal unit—time⁻². The time involved is Δt dp/dt , hence ITT is directly proportional to $\frac{1}{(\Delta t \text{ } dp/dt)^2}$ or $\frac{1}{PEP^2}$. They therefore consider $\frac{1}{PEP^2}$ to be a better correlate of blood flow acceleration than the pre-ejection period of Weissler *et al.*¹⁶

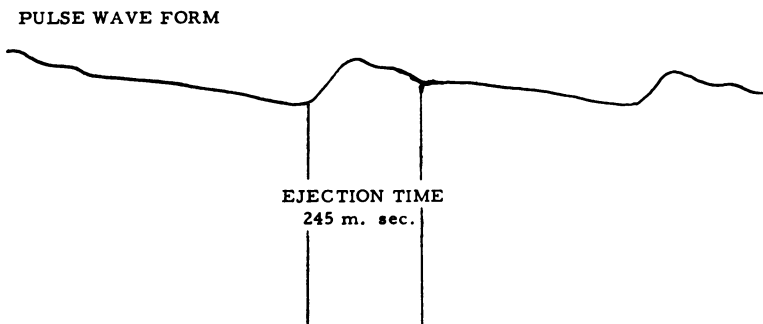
In experimental dogs, Reitan *et al.*¹⁷ compared $\frac{1}{PEP^2}$ to the maximum acceleration of blood in the ascending aorta using electromagnetic flow probes, already shown to be a reliable measurement of cardiac performance¹⁸. They found a close relation between these two measurements in variable heart rates and concluded that the concept of $\frac{1}{PEP^2}$ could be used in clinical situations as a method of monitoring myocardial contractility. While Reitan was in this country we repeated his experiments at the Westminster Hospital using a Biotronex flow probe implanted around the ascending aorta of a dog. Ten days after the implantation of the probe, when the dog seemed recovered and well, the animal was anaesthetized with Halothane and scoline. An aortic cannula was introduced via a femoral artery. Phonocardiogram and electrocardiogram readings were taken. Recordings were made on

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$\frac{1}{PEP^2}$ IS A CORRELATE OF BLOOD FLOW ACCELERATION (REITAN)



$$P.E.P. = 350 - 245 = 105 \text{ m. sec.}$$



$$PRE-EJECTION PERIOD (PEP) = E.M.T. - E.T.$$

Fig. 6. The method of P.E.P. calculation from phonocardiogram, arterial pressure trace and electrocardiogram.

paper and electromagnetic tape. Acceleration of blood in the ascending aorta was calculated only from the tape readings as our pen system was not sensitive enough to record peak acceleration. Variation in PaCO_2 were used to change cardiac output. Figure 7 shows the results of the experiments. Each point on the graph represents ten readings of acceleration and $\frac{1}{\text{PEP}}^2$ taken in a period when conditions were stable. The mean result of each group of ten readings was used to plot the graph.

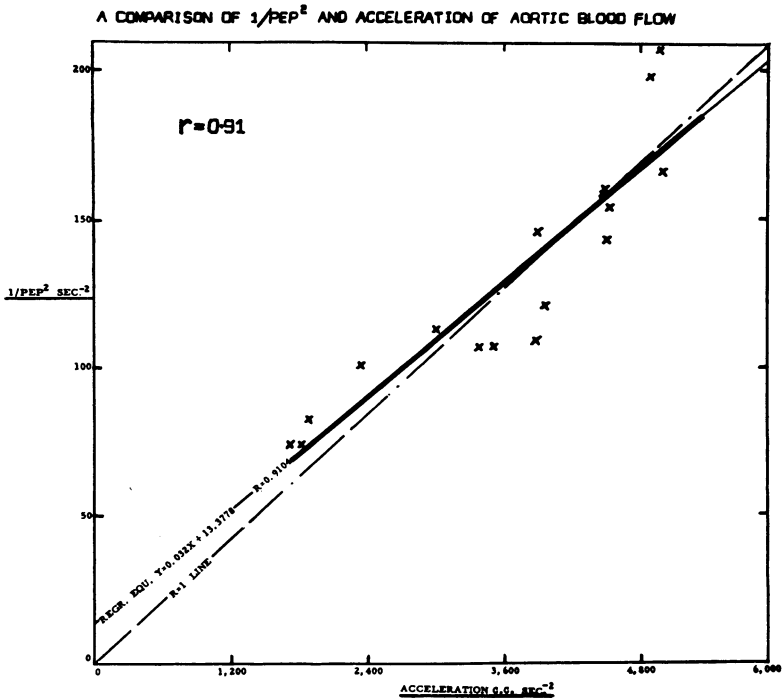


Fig. 7. Results from one dog where $\frac{1}{\text{PEP}}^2$ was plotted against peak acceleration of blood in the ascending aorta.

B. The pre-ejection period used in humans

The most important question of any series of animal experiments must be how relevant are the findings to man? Using the concept of $\frac{1}{\text{PEP}}^2$ on fit patients about to undergo surgical procedures under thiopentone and Halothane anaesthesia, a marked reduction in myocardial contractility was demonstrated using the drugs in clinical dosage. In seven such cases, 2% Halothane reduced myocardial contractility by 60% over 10 to 15 minutes. There was also a prolonged delay exceeding 15 minutes, before recovery occurred. Figure 8 shows two

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such cases studied. These results agree well with the effect of 2% Halothane on the canine heart described earlier. Thiopentone is also shown to depress the human myocardium while diazepam produces little change. PaCO_2 remained constant throughout this investigation.

THE EFFECT OF CARBON DIOXIDE ON CARDIAC PERFORMANCE IN DOGS AND MAN

Increasing carbon dioxide concentrations may depress myocardial contractile force¹⁹. In the intact animal stimulation may also occur, brought about by sympatho-adrenal stimulation²⁰. It was thus important

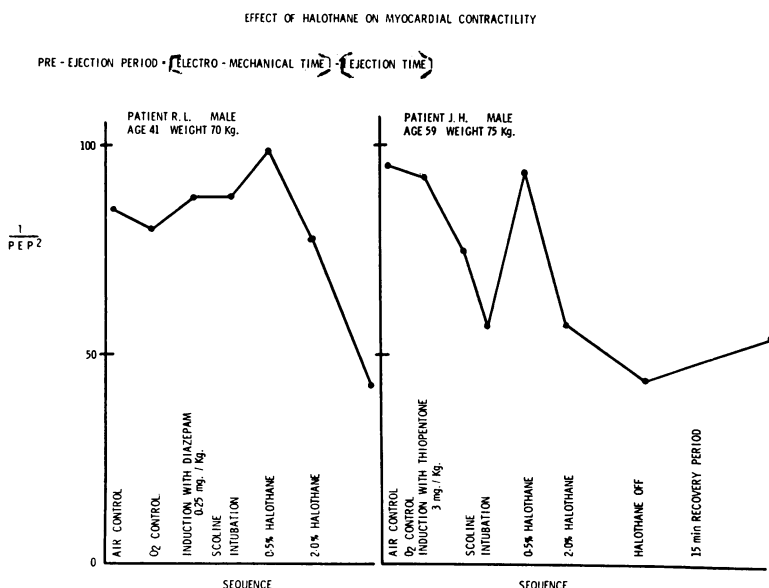


Fig. 8. The effect of Halothane and other anaesthetic agents on $\frac{1}{\text{PEP}^2}$ in human subjects. Both thiopentone and Halothane produce marked myocardial depression. Diazepam and scoline have little effect.

for this study to determine the effect of increasing the partial pressure of carbon dioxide in arterial blood (PaCO_2) on myocardial function. Dogs were initially investigated and myocardial function was measured using a flow probe to determine peak aortic acceleration. In addition the index $\frac{1}{\text{PEP}^2}$ was also measured. In the following graph (Figure 9) $\frac{1}{\text{PEP}^2}$ is plotted against arterial Pco_2 . Initially an increase in PaCO_2 increases myocardial contractility, but beyond a certain point depression occurs. Carbon dioxide concentrations were taken up to the point of depression and then brought down to the previous starting levels. This

THE EFFECT OF CO_2 ON AN ANAESTHETIZED 19 kg. DOG

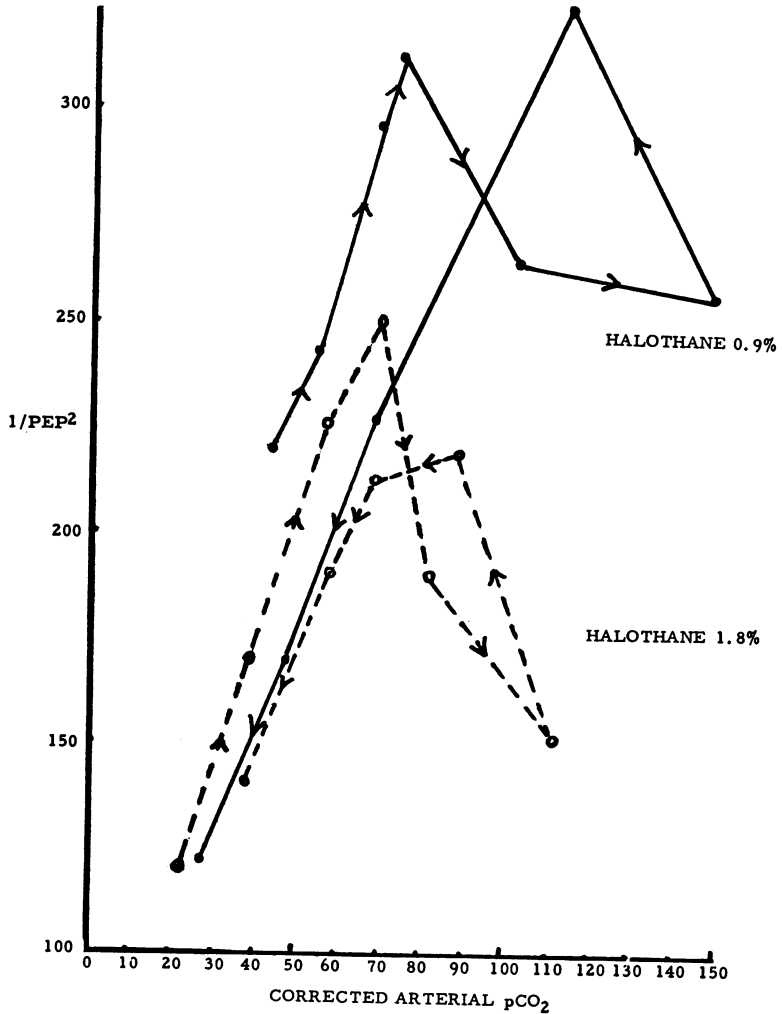


Fig. 9. The effect of changes in PaCO_2 on $\frac{1}{\text{PEP}^2}$ in the anaesthetized dog under MAC 1 Halothane (0.9%) and under MAC 2 Halothane (1.8%). The carbon dioxide myocardial response curve is depressed with increased Halothane.

gives rise to a loop graph as can be seen in the diagram. It is also seen that the higher concentration of Halothane depresses the response to carbon dioxide and the loop obtained is moved to a lower level. This would agree with the theory that Halothane suppresses the release of catecholamines. The initial stimulation to myocardial contractility by increasing PCO_2 can be abolished by the injection of the Beta adrenergic blocking drug, Propranolol. This finding would appear to agree with the postulate that the stimulating effect of CO_2 is brought about by a sympatho-adrenal stimulus. In man it was possible to repeat the foregoing experiments using the $\frac{1}{\text{PEP}}-2$ technique. With an indwelling radial artery cannula for an arterial blood pressure trace, a phonocardiogram and an electrocardiogram, five patients about to undergo surgery were investigated for their response to increased PaCO_2 levels. The patients were induced with small amounts of thiopentone, intubated and respiration was controlled by a ventilator. Anaesthesia was maintained by 0.5% inspired Halothane. Their age range was 28 to 65 years. The results in Figure 10 show a marked increase in myocardial contractility in response to rising PaCO_2 levels. The younger patients gave a much greater response than did the older patients. Of necessity the PaCO_2 levels were not raised above points considered safe.

THE EFFECTS OF HALOTHANE ON HAEMORRHAGE AND HYPOVOLEMIC SHOCK

It has been reported that Halothane anaesthesia is instrumental in preventing surgical shock and also has beneficial effects on patients suffering from hypovolemic shock.

It is well known that the initial adrenergic response to acute hypovolemic hypotension is a vital homeostatic mechanism without which animals and man are less able to tolerate the stresses to which they are subjected. However, it has been observed that sustained sympatho-adrenal activity in such circumstances could be deleterious. Ahlquist²¹ laid the foundation of modern adrenergic receptor concept, nominating two receptors (Alpha and Beta) as the mediators of adrenergic activity. Wiggers *et al.*²² found that the Alpha blocking agent, dibenamine, gave protection against the development of irreversible shock if administered to an animal prior to the onset of haemorrhagic hypotension. Subsequent workers were not able to confirm these findings. With the advent of Beta adrenergic blocking agents, attention was then directed to the rôle of Beta receptor activity in shock. Berk *et al.*²³ suggested that excessive activity is primarily responsible for the deterioration into the irreversible state seen after sustained haemorrhagic hypotension. They claim that Beta adrenergic blockade with propranolol is capable of preventing haemorrhagic pulmonary and splanchnic congestion observed in dogs subjected to haemorrhagic hypotension.

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EFFECT OF RISING P_{aCO_2} ON MYOCARDIAL CONTRACTILITY
IN THE ANAESTHETISED HUMAN (5 SUBJECT)

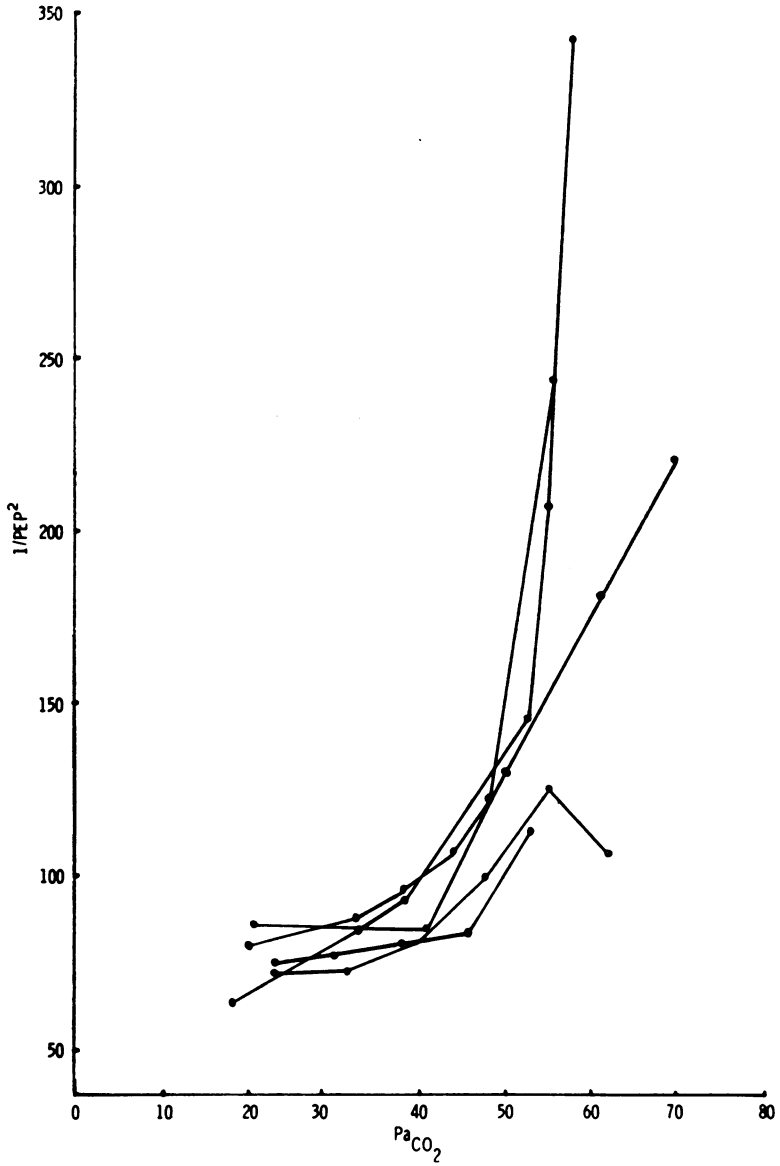


Fig. 10. Myocardial carbon dioxide response curve in five human subjects.

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It has already been stated that Halothane is believed to interfere with the sympathetic response and catecholamine release. For this reason it was decided to carry out a pilot study to determine the reaction of the dog to hypovolemic shock under nitrous oxide and oxygen anaesthesia, 0.75% Halothane anaesthesia and 2.5% Halothane anaesthesia. Six mongrel dogs were used in this investigation. Blood pressure was monitored from the central aorta via a femoral artery cannula. Blood was removed from the dogs by means of a polythene cannula introduced via a femoral vein into the inferior vena cava. A heparinized 20 c.c. syringe was used and, after each 100 c.c. of blood had been withdrawn, five minutes were allowed for stabilization before further

THE EFFECT OF HAEMORRHAGE AND TRANSFUSION ON THE ANAESTHETISED DOG

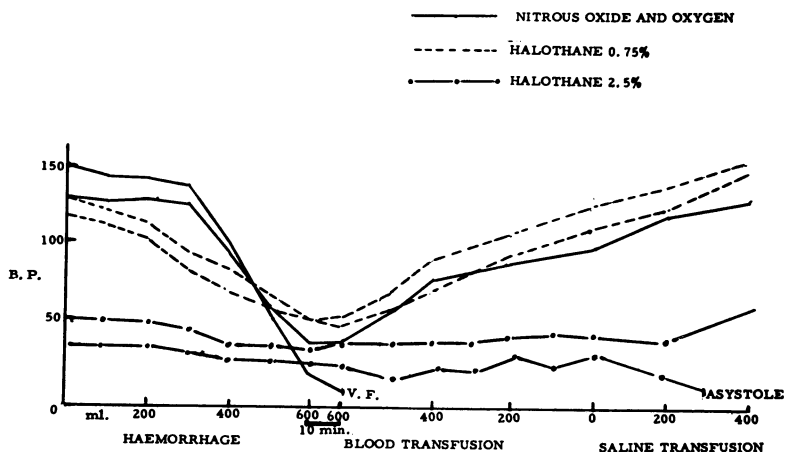


Fig. 11. Blood was withdrawn in 100 c.c. amounts until 600 c.c. had been removed. After a 10-minute period the blood was replaced in 100 c.c. amounts. After it was all returned a saline transfusion was given in 100 c.c. amounts up to 400 c.c.

blood was withdrawn. When nearly half the blood volume had been removed, a 10-minute observation period was carried out and then the heparinized blood returned in the same manner as it had been withdrawn. After returning all the blood, normal saline was transfused in 100 c.c. amounts to a total of 400 c.c. The following Figure 11 shows the response of the mean aortic blood pressure in the six animals under investigation. In the two dogs lightly anaesthetized with nitrous oxide there is a fairly typical response to haemorrhage, blood pressure being reasonably maintained up to a loss of 30% of the blood volume. With further blood loss, pressure fell rapidly, and one of the animals died in ventricular fibrillation. The second dog responded to transfusion

and blood pressure increased. After blood replacement, blood pressure did not return to the control level until after a saline transfusion. In the next pair of dogs, anaesthetized with 0.75% Halothane, the starting blood pressure was significantly lower than the first two. However, the fall in blood pressure was progressive and steady following the fall in cardiac output. Blood pressure did not fall quite as low as in the first pair of dogs and recovery on transfusion was progressive and steady. The blood pressure responded to saline transfusion. Estimating oxygen utilization (which rises rapidly in the hypovolemic shock state) the increase in this figure in the first pair of dogs was twice that achieved in the second pair of dogs.

In the two final dogs, initially deeply depressed with Halothane, there was surprisingly little response to haemorrhage. There was no significant change in blood pressure throughout bleeding and retransfusion. There was a slight increase in blood pressure in one dog in the period of saline transfusion. In the other dog saline produced a further fall in blood pressure and the heart slowed and arrested in asystole. During this experiment there was no demonstrable change in oxygen utilization. These results indicate that it might be of value to study the effects of Halothane on hypovolemic shock more closely as there may be advantages in light Halothane anaesthesia. It would also be interesting to determine whether this method is safer or more effective than Beta adrenergic blockade. Deep Halothane anaesthesia is obviously unsatisfactory in that the animal is markedly depressed and there is poor response to haemorrhage and transfusion.

CONCLUSIONS AND APPLICATION

The most significant effect of Halothane on the canine cardio-vascular system seems to be on the myocardium. Coronary artery blood flow and femoral artery blood flow fall in proportion to the fall in blood pressure and myocardial work. The quantity of oxygen used by the heart also falls by the same amount as the fall in oxygen availability caused by the decrease in blood flow. Oxygen availability was always found to be adequate. Myocardial recovery from 15 minutes Halothane administration is complete after 20 minutes. The recovery of the profoundly depressed heart may be aided by intravenous calcium or isoprenaline. Adrenaline is not recommended. Digoxin was not shown to improve myocardial contractility with Halothane. Propranolol caused more myocardial depression when used with Halothane.

In human subjects the index $\frac{1}{PEP} - 2$ was found to be a reasonably reliable method of measuring myocardial activity under anaesthetic conditions and using this method the human heart was found to suffer the same degree of depression as the canine heart.

Carbon dioxide both directly and indirectly has an important influence on myocardial function. It is postulated that this may be the

main reason why so many differing effects of Halothane on the cardio-vascular system were postulated by previous workers.

The use of Halothane in hypovolemic shock is considered. It is suggested that it may possess a protective effect. Deep Halothane anaesthesia is not recommended.

While Halothane is well tried in clinical practice and favourably accepted by most anaesthetists, it is important that its cardio-vascular effects are underlined in relation to special circumstances:

1. Venous thrombosis

While there is yet no evidence that the type of anaesthesia plays a part in deep venous thrombosis in the legs and pelvis on the operating table or in the incidence of postoperative pulmonary embolism, it must be pointed out that there is little work recorded in the literature relating the depth and type of anaesthesia to subsequent venous thrombosis; there is certainly a need for further clinical studies on this subject. One of the problems in such investigation is the multiplicity of contributory causes to venous thrombosis, such as damage to the veins, length and type of operation, age of the patient, etc. It might well be that reduced blood flow due to anaesthesia could play a part. Hypotensive anaesthesia is frequently used to reduce blood loss in major surgery and it would certainly be of great interest to see if this factor alone significantly increased the incidence of thrombotic problems particularly in the more elderly patient.

2. Arterial thrombosis

In all forms of arterial surgery the success of the operation depends to a large extent upon an adequate flow through the anastomosis or past an arterial suture line. Much reduced flows will play an important part in the failure of such procedures.

3. Cardiac surgery

(a) *Cardiac catheters.* General anaesthesia is frequently used in cardiac catheterization, particularly in infants. Such infants are frequently induced with Halothane anaesthesia. Occasionally, pronounced depression of blood pressure and cardiac output occurs, together with some depression of oxygen consumption. Such changes can give rise to misleading and incorrect interpretation of the results.

(b) *Cardiac operations.* It is obviously important to the cardiac surgeon to appreciate that Halothane and other negative inotropic drugs may depress the myocardium. After anaesthesia circulatory arrest may be necessary to operate on the heart. Following the operative procedure the heart must be restarted. It seems reasonable that myocardial depression should be minimal at this time. If the heart fails to

start spontaneously or with electric shock, then calcium, adrenaline and isoprenaline are frequently used in an empirical manner.

4. Cerebral blood flow

Clinical experience has shown that the central nervous system tolerates Halothane-induced hypotension, usually without any problem.

Against the disadvantages discussed, Halothane has proved to be a safe anaesthetic with world-wide use. However, like many things in life, I would like to stress greater need for moderation in the dose administered which many practising anaesthetists have observed for some time. One invariably finds the wise man doing the right thing and the research worker finding out why he is wise.

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